The Effect of Naltrexone on Alcohol’s Stimulant Properties and Self-Administration Behavior in Social Drinkers: Influence of Gender and Genotype

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Background: Few pharmacological treatments for alcohol dependence are available. Moreover, the best supported treatment, naltrexone hydrochloride, appears to work for only some.

Methods: To investigate potential predictors of these differential responses, 40 social drinkers (20 women) were administered 6 days of treatment with naltrexone vs. placebo in a double-blind, counterbalanced, crossover design. At the end of each treatment period, participants received a single dose of their preferred alcoholic beverage followed by the opportunity to work for additional alcohol units using a progressive ratio (PR) breakpoint paradigm. All subjects but one were genotyped for the A118G polymorphism of the mu opioid receptor gene (OPRM1).

Results: Naltrexone decreased the ethanol-induced ‘euphoria’ to a priming dose of alcohol in two subgroups: (i) in women, and (ii) in subjects with the A118G polymorphism of the mu opioid receptor gene (OPRM1). Naltrexone did not decrease motivation to work for additional alcoholic beverages on the PR task regardless of gender or genotype.

Conclusions: The results add to the evidence that naltrexone decreases positive subjective effects of alcohol, with preferential effects in distinct subgroups. Similar effects in heavier drinkers might decrease alcohol use.

Key Words: Alcohol Dependence, Opioids, Addiction, Individual Differences.

EXTHANOL ADMINISTRATION INDUCES the release of endogenous opioids in laboratory rodents (Marinelli et al., 2003, 2005) and in humans (Dai et al., 2002). Conversely, administration of the opioid receptor antagonist, naltrexone (Revia), has been reported to decrease alcohol’s positive subjective effects and drinking behavior. For example, in alcohol-dependent patients, naltrexone has been found to decrease alcohol intake and the ability of alcohol exposure to precipitate binges (Anton et al., 2004; Berglund, 2005; Drobes et al., 2003; Feinn and Kranzler, 2005; O’Malley et al., 1992; Oslin et al., 1999; Volpicelli et al., 1992). In laboratory studies conducted in heavy social drinkers, naltrexone can diminish subjective stimulant effects of alcohol and the urge to drink (Davidson et al., 1999; King et al., 1997; Na and Lee, 2002; Peterson et al., 2006; Ray and Hutchison, 2007; Swift et al., 1994). However, although the majority of reported clinical trials indicate positive effects of naltrexone, there are also multiple negative reports (Krystal et al., 2001; Killeen et al., 2004; O’Malley et al., 2007; though, for a reanalysis of two negative findings, see Gueorguieva et al., 2007). Laboratory studies in social drinkers have also yielded inconsistent results; naltrexone failed to decrease ad lib alcohol ingestion in two studies (Davidson et al., 1996; Drobes et al., 2003) while the significant effects seen in two others were proposed to reflect nonspecific sedation and nausea (Davidson et al., 1999; de Wit et al., 1999).

Some of the above discrepant findings might be explained by different effects in subpopulations. For example, a retrospective analysis of an existing dataset suggested that naltrexone may be clinically more effective in women than men (Kiefer et al., 2005). Although this was not replicated in two subsequent retrospective analyses (Baros et al., 2008; Greenfield et al., 2010), preferential effects were seen in women in the one prospective study reported to date (Tidey et al., 2008).

A second potential predictor of differential responses to naltrexone is genetic variation of the OPRM1 gene that encodes for the mu opioid receptor. The most common variant is the A118G single nucleotide polymorphism, which results in an amino acid substitution of Asn40Asp (Bergen et al., 1997). This mutation has been reported to enhance alcohol-induced positive subjective effects and craving responses in nondependent users (Ray and Hutchison, 2004;
van den Wildenberg et al., 2007) and is associated with greater effects of naltrexone in both social drinkers (Ray and Hutchison, 2007) and alcohol abusers (Oslin et al., 2003; Anton et al., 2008; though, see also Gelernter et al., 2007; Tidey et al., 2008).

To address these issues further under controlled laboratory conditions, we tested the effects of naltrexone in a sample of male and female social drinkers genotyped for polymorphisms of the mu opioid receptor. Alcohol self-administration behavior was measured using a progressive ratio (PR) breakpoint paradigm, an objective behavioral measure of motivation to seek reward (Barrett et al., 2006, 2008). Positive and other subjective effects of alcohol were measured with self-report questionnaires.

MATERIALS AND METHODS

Subjects

Forty-two healthy, medication-free, social drinkers entered the study. The participants were healthy social drinkers, aged 18–50 who ingested a minimum of 5 alcoholic units per week (1 unit = 1.5 oz of 80-proof alcohol; 12 oz of beer; 5 oz of wine) and scored ≤5 on the MAST. Participants were excluded for any of the following: current or past dependence on substances other than nicotine or caffeine; current major axis I psychiatric disorder; past major axis I psychiatric disorders except unipolar mood or anxiety disorders in current, sustained, medication-free remission; cardiovascular, neurological, or other disorders that might be aggravated by participation in the study or complicate interpretation of the study’s results (e.g., liver enzymes ≥ 2.5 times above normal, abnormal ECG; body mass index ≤ 19 or > 26); acute hepatitis, liver failure, or other liver disorders that might be aggravated by alcohol and/or naltrexone exposure; subjects currently taking opioid analgesics or other opioid containing medications; and, in women, a positive pregnancy test or not using a reliable method of birth control.

Participants were recruited using a three-stage identification procedure. (i) Volunteers were initially screened during a semi-structured telephone interview. (ii) Those who were interested and tentatively met the entry criteria were invited to a face-to-face interview using the Structured Clinical Interview for DSM-IV (SCID, First et al., 1995) and the Michigan Alcohol Screen Test (MAST, Pokorny et al., 1972) a brief measure of lifetime alcohol problems indicative of possible abuse or dependence. (iii) Volunteers underwent a physical examination by a physician at the Medisys clinic, who determined whether subjects met inclusion/exclusion criteria, with laboratory tests as deemed appropriate, to ensure that they were medically safe to participate. Two female participants withdrew from the study after completing 1 and 3 days of the first week, respectively. Both had been taking naltrexone, and both cited nausea and general malaise as the reason for discontinuing participation. Follow-up confirmed full recovery within 48 hours. The study was approved by the Royal Victoria Hospital Research Ethics Board. All participants provided written informed consent.

Design

The study was a double-blind, randomized, placebo controlled, counter-balanced, crossover design. Participants received oral naltrexone (with a 50 mg riboflavin marker) or riboflavin alone in identical capsules for 6 days. On Day 1 of the active treatment phase, subjects took 25 mg of naltrexone. If adverse side effects did not occur, subjects took 50 mg per day for the remaining 5 days. Side effects of the drug were monitored after the initial dose, midway through the regimen and at the start of each test session using a Symptom Check List (SCL) including “headache,” “nausea/vomiting,” “fatigue,” and “abdominal cramps.” Participants rated severity of each symptom on a 5-point rating scale from “not at all” to “severe.”

On the sixth day of each treatment, participants arrived at noon at our Clinical Research Unit for their test day. Participants were asked to abstain from alcohol for at least 24 hours before the test session and to abstain from nicotine and caffeine on the test day A breathalyzer confirmed abstinence from alcohol. Urine screens confirmed compliance with the treatment regimen (all participants had visually detectable riboflavin under UV light, 366 nm) (Del Boca et al., 1996). All subjects tested negative on a urine drug screen sensitive to cocaine, opiates, phencyclidine, barbiturates, A1-tetrahydrocannabinol, benzodiazepines, and amphetamines (Triage Panel for Drugs of Abuse; Biosite Diagnostics, San Diego, CA). All women tested negative on a urine hCG test. Crossover occurred after a minimum 7-day washout period. In women, both drug regimens and test days took place during the follicular phase of their cycle or during the placebo week of their oral contraceptive pill.

Alcohol Self-Administration Task

The alcohol self-administration paradigm followed the same procedures as used in our previous studies (Barrett et al., 2006, 2008). Subjects performed all tasks individually to rule out the social aspect of drinking, except for the presence of one of the researchers. At 2:00 pm, subjects received a priming drink (their preferred 80-proof alcohol beverage mixed with caffeine-free soda or juice) to normalize drinking in the laboratory setting and to measure the response to a standard ethanol unit (males: 12 g; females: 10.4 g). The lower dose for women was to compensate for sex differences in ethanol pharmacokinetics (Baraona et al., 2001). Subjects were then offered the opportunity to work for up to 10 additional drinks, each containing half the standard unit of alcohol (males: 6 g; females: 5.2 g) vs. water, on a computerized PR schedule. The PR breakpoint paradigm was used as an objective, behavioral measure of motivation to obtain alcohol. Subjects were offered the option of drinking more alcohol, water, or neither. To receive one extra drink (water or alcohol), participants were required to press keys on a computer keyboard 40 times. To receive a second drink required pressing 60 times. Up to a maximum of 10 selections from each drink category (water and alcohol) was permitted (PR = 40, 60, 90, 135, 203, 304, 456, 684, 1,026, 1,538 key presses) although participants were not informed of the maximum. The maximum alcohol load was 1.25 mL/kg. The session proceeded as follows:

1. Participant fills in subjective state scales.
2. Participant exposed to glass of water (sight, smell).
3. Participant fills in subjective state scales.
4. Participant exposed to favorite alcoholic beverage (sight, smell).
5. Participant fills in subjective state scales.
6. Participant asked to have one drink of favorite alcoholic beverage (sight, smell).
7. Participant rests for 15 min, filling in subjective state scales.
8. Participant can button press to choose one of 3 possibilities: (i) Another alcoholic beverage, (ii) Water, or (iii) No beverage (if option (i) or (ii) chosen, participant was allowed to consume and finish the drink at their own pace but could not begin to button press for a subsequent drink of the same kind until the previous drink was completed)
9. Repeat step 8 up to maximum of 10 “earned” alcoholic drinks OR remain seated to the time limit of 2 hours (neither detail was disclosed to the participant).

Participants were required to remain seated in front of the keyboard until they had earned the maximum number of alcoholic drinks or the 2-hour time limit had elapsed, whichever came first. After completing the procedure, subjects were required to remain
on-site until their blood alcohol level was below 0.04% at which time they were provided with a taxi home.

**Subjective Desire for Alcohol.** Subjective desire for alcohol was assessed throughout the test session. Two visual analogue scales (VAS), anchored at 1 = “Least” to 10 = “Most,” were labeled Want a drink and Desire a Drink. Participants were instructed to assess how they were feeling at each time referencing the “least or the most they could ever imagine feeling that way” to avoid ceiling or floor effects.

**Subjective Effects of Alcohol.** Subjective effects induced by alcohol were measured with the Subjective High Assessment Scale (SHAS, Schuckit et al., 1997), and 11 VAS labeled Like the Drink, Sedated, Intoxicated, Euphoria, Mind Racing, Alert, Energetic, Excited, Rush, Anxiety, and High. SHAS items were examined individually as analogue scales anchored at 0 = “normal” to 10 = “extremely”. Participants’ markings were measured in mm and calculated as a percentage of the whole scale (54 mm). All items were assessed individually as the authors wished to examine the stimulatory and sedative effects of alcohol separately.

### DEPENDENT MEASURES

**Subject Characterization**

**Genotypes.** DNA, extracted from venous blood by the phenol-chloroform method, was available for 39 participants. The A118G polymorphism of the mu opioid receptor gene (OPRM1) was genotyped according to the methods described by Bergen and colleagues (1997). Amplification at an annealing temperature of 66°C, using forward primer 5'CCTTGGCGTACTCAAGTTGCTC3 and reverse primer 5'TTCGGACC CATGGGACCGAC3, produced a 95-bp product. After overnight digestion with Drd1, samples with a G substitution (Asn 40) were cleaved into 22- and 73-bp fragments. Ethidium bromide-stained fragments were resolved on 5% polyacrylamide gels and photographed under UV. All samples were amplified and were typed unambiguously with 100% inter-rater reliability (2 raters). The allele frequencies of 0.128 G and 0.872 A were not significantly different from those reported in Caucasian populations (Bergen et al., 1997; Gelernter et al., 1999) and genotype frequencies were in Hardy–Weinberg equilibrium (0.026 GG, 0.205 GA, 0.769 AA).

Because previously characterized control samples were not available, Hardy–Weinberg equilibrium was applied where appropriate. ANCOVAs were performed to rule out the effects of nausea, side effects, and individual patterns of alcohol use. Correlations were calculated using Pearson’s correlation coefficients.

### RESULTS

#### Subject Characteristics

As summarized in Table 1, subjects were nondependent social drinkers. As a group, the participants averaged 15.5 ± 1.5 drinks per week. Men reported significantly more drinks per current drinking episode than women (mean ± SEM, men: 7.0 ± 0.9; women: 4.8 ± 0.4, p < 0.05). There was a trend for the OPRM1 -/G allele carriers to report consuming fewer alcohol units per week during their heaviest period of drinking than individuals with the A/A genotype (A/A, 22.0 ± 1.9; -/G, 14.9 ± 2.6, p < 0.10). There were no other group differences when subjects were separated by gender or genotype.

#### Side Effects of Naltrexone

Side effects of headache, nausea/vomiting, fatigue, and abdominal cramps/pain were measured at the beginning of each test session with the SCL. A total side effect score including all four symptoms was calculated. There were no main effects of naltrexone treatment or any main or interaction effects with gender on any of the measures. In comparison, OPRM1 G-allele carriers reported significantly more side effects of naltrexone compared to placebo whereas the A/A homozygotes had the opposite pattern at a trend level (Drug × Gene, $F_{1,28} = 3.5, p < 0.01$, -/G OPRM1: Pbo, 0.9 ± 0.4, Nal, 1.5 ± 0.3, p < 0.05; A/A OPRM1: Pbo, 0.7 ± 0.4, Nal, 1.3 ± 0.3, p = 0.3).

### Table 1. Breakdown of Participants by Gender and OPRM1 Genotype of A118G Polymorphism

<table>
<thead>
<tr>
<th>Gender</th>
<th>Women (20)</th>
<th>Men (20)</th>
<th>Totals (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM1 genotype</td>
<td>14 (A/A)</td>
<td>16 (A/A)</td>
<td>30 (A/A)</td>
</tr>
<tr>
<td>Age</td>
<td>21.7 ± 1.0</td>
<td>22.0 ± 1.9</td>
<td>21.9 ± 0.6</td>
</tr>
<tr>
<td>Age of first alcohol intoxication</td>
<td>15.1 ± 0.5</td>
<td>15.9 ± 0.5</td>
<td>15.5 ± 0.3</td>
</tr>
<tr>
<td>Current alcohol units/wk</td>
<td>12.8 ± 1.4</td>
<td>16.3 ± 1.8</td>
<td>15.5 ± 1.5</td>
</tr>
<tr>
<td>Heaviest period alcohol units/wk</td>
<td>20.2 ± 2.9</td>
<td>23.6 ± 2.6</td>
<td>21.3 ± 1.8</td>
</tr>
<tr>
<td>Current drinking episodes/wk</td>
<td>2.6 ± 0.7</td>
<td>2.9 ± 0.5</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Current alcohol units/drinking episode*</td>
<td>4.8 ± 0.4</td>
<td>5.8 ± 0.6</td>
<td>5.9 ± 0.5</td>
</tr>
<tr>
<td>Lifetime alcohol intoxications</td>
<td>236 ± 51</td>
<td>259 ± 65</td>
<td>252 ± 36</td>
</tr>
<tr>
<td>MAST</td>
<td>0.8 ± 0.2</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.1</td>
</tr>
</tbody>
</table>

MAST, Michigan Alcoholism Screening Test.

*One participant homozygous OPRM1 G/G. Numbers represent mean ± SEM.

*One participant (male) not genotyped.

*Significant effect of gender, p < 0.05.
Subjective nausea was also measured with the SHAS item, “nauseous” at four times: (1) before any drinks (start); (2) after seeing the water (see water); (3) after seeing the alcohol (see alcohol); and (4) after drinking the priming dose of alcohol (drink alcohol). There was a significant Drug × Gender × Time interaction on ratings of “nauseous” (\(F_{3,91} = 3.1, p < 0.05\)). Here, OPRM1 A/A women experienced more nausea at the beginning of the naltrexone session than the placebo session (start: Pbo, 0.00 ± 0.02; Nal, 0.02 ± 0.02; \(p < 0.05\)). While women with the G-allele reported feeling more nauseous after consuming the priming dose of alcohol during the naltrexone session when compared to placebo (drink alcohol: Pbo, 0.00 ± 0.04; Nal, 0.08 ± 0.05; \(p < 0.05\)). Men did not report any significant changes in nausea because of naltrexone at any time over the test sessions. Based on these observations, the total SHAS “nauseous” scores over the naltrexone session were also used as covariates in subsequent analyses.

Effects of Naltrexone on Subjective Ratings

Given the imbalance of women in the G-allele group (6 of 9) as well as a disproportionate number that received placebo on the first session (7 of 9), we examined subjective ratings in 5-way ANCOVAs (Drug × Gene × Gender × Time × Order). Means are expressed as the adjusted means (±SEM) after including the covariates of total side effects (from SCL) and total SHAS “nauseous” ratings from the naltrexone session.

For “euphoria,” the ANCOVA yielded significant Drug × Gender × Time (\(F_{3,81} = 3.0, p < 0.05\)) and Drug × Gene × Time interactions (\(F_{3,81} = 2.9, p < 0.05\)). In women, naltrexone decreased “euphoria” after both seeing and drinking the priming dose of alcohol compared to ratings during the placebo session [Fig. 1A, see alcohol: Pbo, 1.5 ± 0.2 (adjusted mean ± SEM); Nal, 1.0 ± 0.2, \(p < 0.05\); drink alcohol: Pbo, 2.1 ± 0.3; Nal, 1.3 ± 0.4, \(p < 0.05\)]. Men did not report differences in “euphoria” between the naltrexone and placebo sessions at any time (Fig. 1B, \(p > 0.2\)). Carriers of the G-allele also experienced decreased “euphoria” during the naltrexone session after seeing and drinking the alcohol priming dose when compared to placebo (Fig. 1C, see alcohol: Pbo, 1.6 ± 0.3; Nal, 0.9 ± 0.3; \(p < 0.05\); drink alcohol: Pbo, 2.3 ± 0.3; Nal, 1.1 ± 0.5; \(p < 0.05\)), whereas this was not seen in the OPRM1 A/A participants (Fig. 1D, \(p > 0.2\)). Although there were no Gene × Gender interactions, visual comparison of the marginal means suggested that naltrexone-induced reductions in “euphoria” were more pronounced in OPRM1 -/G women than in OPRM1 A/A women and -/G men (-/G women: see alcohol: Pbo, 1.8 ± 0.4; Nal, 0.8 ± 0.3; drink alcohol: Pbo, 2.6 ± 0.4; Nal, 0.9 ± 0.7; A/A women: see alcohol: Pbo, 1.3 ± 0.3; Nal, 1.2 ± 0.2, drink alcohol: Pbo, 1.6 ± 0.3; Nal, 1.6 ± 0.4; -/G men: see alcohol: Pbo, 1.3 ± 0.5; Nal, 1.2 ± 0.4, drink alcohol: Pbo, 1.6 ± 0.6; Nal, 1.6 ± 0.9).

**Fig. 1.** Effects of naltrexone on visual analogue scale (VAS) “euphoria” by gender and OPRM1 genotype. Placebo (grey diamonds) vs. naltrexone (black squares) in women, \(N = 19^a\) (A), men, \(N = 17^{bc}\) (B), and participants with OPRM1 -/G, \(N = 9\) (C) or OPRM1 A/A, \(N = 27\) (D). *Post hoc comparison \(p < 0.05\) difference from placebo. *One participant missing “euphoria” measure; *two participants missing Symptom Check List measures; *one participant not genotyped.
Analysis of SHAS “high” ratings resulted in significant Drug × Gender × Gene × Time ($F_{3,84} = 2.8, p < 0.05$) and Drug × Gene × Time × Order ($F_{3,84} = 2.8, p < 0.05$) interactions after adjusting for nausea and side effects. Post hoc comparisons showed a significant naltrexone-induced reduction in SHAS “high” in G-allele women after consuming the priming dose of alcohol (Fig. 2A, drink alcohol: Pbo, 0.04 ± 0.05; Nal, −0.02 ± 0.04; $p < 0.01$). This decrease was not significant in any other subgroup (at drink alcohol: A/A women, Pbo, 0.08 ± 0.03; Nal, 0.07 ± 0.02; A/A men, Pbo, 0.02 ± 0.06; Nal, 0.03 ± 0.05), and there were no other significant contrasts (Fig. 2B, C, D). However, the Drug × Gene × Time × Order interaction indicated that only G-allele carriers that received placebo on the first day experienced a reduction in the alcohol-induced “high” because of naltrexone (drink alcohol: Pbo, 0.07 ± 0.04; Nal, 0.02 ± 0.03; $p < 0.01$). Taken together, this would suggest that primarily the OPRM1 -/G women who received naltrexone on the second session experience a reduced “high” after consuming the alcohol. However, this decrease in alcohol-induced “high” was not observed in any other gene by gender combination that received naltrexone on the second day, suggesting the preferential effect in the G-allele women was not merely an artefact of order.

Consumption of the alcohol priming dose increased subjective intoxication without any significant main effects or interactions because of naltrexone, gender, or genotype (VAS “intoxicated”: main effect of Time, $F_3 = 4.3$, $p < 0.01$; start, 1.2 ± 0.1; see water, 1.2 ± 0.1; see alcohol, 1.2 ± 0.1; drink alcohol, 2.2 ± 0.2, $p < 0.001$ for drink alcohol rating compared to all other times). There were no significant effects of Drug or Drug interactions on any of the remaining subjective effects evaluated.

Effects of Naltrexone on Alcohol Self-Administration

In the group as a whole, the earned alcoholic drinks during the test sessions were related to substance use outside of the laboratory. The greater the number of alcoholic drinks worked for on either session, the greater the lifetime use of alcohol and the amount of alcohol used during the week prior to the beginning of each treatment regimen (previous week drinking: Pbo, $r = 0.402$, $p < 0.05$; Nal, $r = 0.503$, $p < 0.01$; lifetime alcohol: Pbo, $r = 0.338$, $p < 0.05$; Nal, $r = 0.365$, $p < 0.05$).

Analyses of alcohol self-administration on the PR task did not yield any significant effects of naltrexone on breakpoints or total number of presses for alcoholic drinks. Covarying nausea, side effects, and variations in individual alcohol use (current drinks per drinking episode, current drinks per week, heaviest period drinks per week, lifetime alcohol intoxications) did not reveal any significant effects. There were no significant interactions with either gender or genotype ($p ≥ 0.3$).

DISCUSSION

The present study has three main findings. First, it replicates a now fairly consistent finding that naltrexone can diminish stimulant and euphoric effects of alcohol.
Second, it adds to a smaller literature suggesting that these effects occur preferentially in women and carriers of the G-allele for the mu opioid receptor gene, OPRM1; those with both of these traits might be the most sensitive. Third, the results do not support the hypothesis that these decrements in subjective effects translate to decreased self-administration behavior in moderate social drinkers.

The majority of clinical trials with mu opioid receptor antagonists find evidence of decreased alcohol use; however, the group effects have been weak, seeming to occur in some patients only (Bouza et al., 2004; Gueorguieva et al., 2007; Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2005; Streeton and Whelan, 2001). Preliminary evidence suggests that some of this variability is attributable to genetic variation of the OPRM1 gene (Anton et al., 2008; Oslin et al., 2003). This possibility was supported by an initial laboratory study in moderate to heavy social drinkers; G-allele carriers exhibited a greater naltrexone-induced reduction in alcohol’s stimulant and pleasurable effects (Ray and Hutchinson, 2007). The present study provides a first laboratory replication.

Gender has also recently emerged as a possible moderator of naltrexone’s effects. The possibility that naltrexone might be more efficacious in women than men was first suggested by a retrospective analysis of clinical trial data (Kiefer et al., 2005). In support, a subsequent prospective study in nontreatment-seeking heavy drinkers suggested that naltrexone decreased alcohol’s stimulant effects in women only (Tidey et al., 2008). In comparison, other clinical trials (Baros et al., 2008; Greenfield et al., 2010) and laboratory studies (Davidson et al., 1999; Drobes et al., 2003) suggest that naltrexone can be more efficacious in women than men.

The observation that women with the A118G polymorphism appear the most sensitive to naltrexone’s effects should be considered preliminary. The subsamples were small, and the interaction was influenced by an order effect in the case of SHAS “high”. This noted, visual inspection of the “euphoria” data also suggested that the naltrexone-induced reductions occurred primarily in women with the OPRM1 -/G polymorphism. Replication in future studies with larger samples of men and women G-allele carriers is required but may help explain, in part, negative findings in clinical trials when gender or genotype effects were examined separately.

Finally, our results do not support the proposition that naltrexone can decrease alcohol self-administration in social drinkers, even in subgroups that reported diminished positive subjective effects. Previous work is consistent with this observation. For example, Drobes and colleagues (2003) reported that naltrexone decreased ad lib drinking in alcohol-dependent subjects but not in social drinkers. Similarly, naltrexone failed to decrease ad lib alcohol ingestion in Davidson et al. (1996) while the significant effects seen in two other studies were thought to reflect nonspecific sedation and nausea (Davidson et al., 1999; de Wit et al., 1999). The present study further suggests that naltrexone does not diminish self-administration behavior in social drinkers and extends the findings to the use of a PR breakpoint paradigm.

Like all studies, this one is not without limitations. First, some of the subjects experienced naltrexone-induced nausea, particularly those carrying the G-allele. However, only 5% of participants withdrew from the study, and neither nausea nor other side effects accounted for significant variance in the observed changes in subjective response to alcohol. Second, the G-allele subgroup was small and not counterbalanced. However, the population frequency was as seen in other samples (Gelernter et al., 1999; Oslin et al., 2003), and including order in the statistical model still yielded preferential effects in the G-allele carriers. Indeed, the results replicate quite closely Ray and Hutchinson’s (2007) report that naltrexone reduces alcohol’s stimulatory and positive subjective effects preferentially in social drinkers who carry the G-allele (n = 40, 15 G-allele carriers). Third, the PR breakpoint paradigm has been used by us successfully before (Barrett et al., 2006, 2008; Venugopalan et al., 2009) but it remains a laboratory model with attendant artificial aspects (Davidson et al., 1999). Despite this, individual differences in alcohol ingestion were well predicted by alcohol use on the street, suggesting that the PR breakpoint measure has validity, demonstrating good sensitivity to individual differences in substance use patterns. The ability to detect naltrexone-induced reductions in alcohol consumption may be limited to a heavier drinking population (Drobes et al., 2003). Fourth, changes in subjective effects were primarily detected post consumption of the priming dose of alcohol. These results were not unexpected; naltrexone may be diminishing the effects of ethanol-induced opioid release (Dai et al., 2002; Marinelli et al., 2003, 2005). In previous studies, naltrexone affected responses to alcohol but not placebo beverages or pre-alcohol measures (Ray and Hutchinson, 2007; Swift et al., 1994).

In conclusion, the present laboratory study in moderate social drinkers supports the evidence from heavy and dependent drinking populations that naltrexone reduces alcohol’s positive subjective effects and that gender and OPRM1 genotype moderate these effects. These naltrexone-induced changes in subjective experience, though, did not translate to decreased alcohol self-administration in this population. Additional studies in large, prospectively genotyped, heavier drinking populations may elucidate further naltrexone’s effects on motivation to obtain alcohol as well as the influence of gender and OPRM1 genotype.

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